REMARKS/ARGUMENTS

After entry of this paper, claims 21, 25 and 30-54 are pending. Claims 1-20, 22-24, and 26-29 are canceled. Claims 1 and 8-19 are canceled without prejudice, as being drawn to non-elected subject matter. Applicants reserve the right to prosecute the non-elected claims and subject matter voluntarily removed from the pending claims in a divisional or continuation application filed during the pendency of the present application. Claims 21 and 25 are amended. Claims 30-54 are newly added.

Support for the Amended Claims

Support for the amended and newly added claims is found in the specification as follows, as well as in the previously pending claims:

Claim Number	Support in Specification
21	Page 20, line 24 through page 21, line 4; pg. 33, l. 17-20;
25	Pg. 29, lines 6 et seq.;
30, 40	Pg. 21, line 27-pg. 22, l. 2 and 28-pg. 23, l. 4
31, 41	Pg. 22, l. 2-24
32, 42	Pg. 34, l. 12-15
33	Pg. 36, l. 9-10
34-36 44-46	Page 51, lines 19-page 53, line 2; page 25, lines 24-page 26, line 1; Figs. 7A and 7B, Example 8
37, 43	Fig. 2A, Fig. 5; pg 9, lines 26-30; pg. 13, lines 4-8; page 20, line 24 through page 21, line 4
38	Pg. 32, line 14 et seq.
39	Pg. 29, l. 28-29; pg. 30, l. 4
47	Pg. 26, l. 13 – pg. 27, l. 24
48	Pg. 29, lines 16-27
49	Pg. 15, l. 20-pg. 16, l. 5; p. 19, l. 11-14; pg. 23, l. 10 - pg. 25, l. 11
50	page 16, lines 17-20; pg. 19, line 27 et seq.;
51	Figs. 2A and 5 and page 9, lines 26-30
52	Original claim 2; pg. 19, l. 17-23
53	Fig. 5 and page 16, lines 7-20; page 12, lines 1-10
54	Pg. 15, l. 20-pg. 16, l. 5; p. 19, l. 11-14; pg. 23, l. 10 - pg. 25, l. 11

Applicants have amended the specification to correctly note that US Patent Application No. 09/994,192 is now US Patent No. 6,610,306.

No new matter is added by these amendments.

Statement of the Substance of the Interview

Applicants hereby express their appreciation to the examiner for the courtesy of the interview granted on November 8, 2005 to Applicants' undersigned representative. The recordation of the substance of the interview is provided by the remarks hereinbelow and also as presented in the arguments addressing the outstanding rejections below:

(1) *a brief description of the nature of any exhibit shown or demonstration conducted*: NONE

(2) *an identification of the claims discussed*: claims 2-7, 17, 18, 21-29

(3) *an identification of specific prior art discussed*: Manning *et al*, Microb. Pathogen., 25:11-22 (1998); International Patent Publication No. WO 94/12641 (Chong); and briefly the items listed in the Office Action under "relevant art", i.e., Kawarabayasi *et al*, **1998** DNA Res., 5:55-76 and Albertini *et al*, **1991** J. Bacteriol, 173:3573-3579.

(4) *an identification of the principal proposed amendments of a substantive nature discussed*: We discussed the amendment of claim 21 primarily with regard to the terms and phrases "homolog" and "at least 8 amino acids" and what support existed for same in the specification. We discussed possible method claims.

(5) *a brief identification of the general thrust of the principal arguments presented to the examiner*: These arguments are presented fully below in this response and related to similarity of SEQ ID NO: 2 and SEQ ID NO: 4 and whether antisera to these sequences would be expected to behave in a predictable and similar manner. We discussed support in the specification for the terms used in the claims, and use of *In re Katz* and Rule 132 declarations to possibly overcome some of the other rejections.

(6) *a general indication of any other pertinent matters discussed*: We discussed anti-meningococcal vaccines in general.

(7) *the general results or outcome*: No agreement was reached. The examiner indicated that she would consider further evidence or amendments placed before her by this response.

Specification Informalities

The cross-reference to the related applications is objected to for failure to note the issuance of US Patent No. 6,610,306.

The specification is objected to as failing to provide proper antecedent basis for the limitation "polypeptide comprises amino acids 1 to 178 of SEQ ID NO: 4" in claims 7 and 29.

Applicants respectfully request withdrawal of these objections in view of the specification amendment above and cancellation of claims 7 and 29.

However, Applicant directs the examiner's attention to the fact that this application specifically teaches an OMP85 protein and refers to both the homologs of that protein from *N. meningitidis* of SEQ ID NO: 4 and *N. gonorrhoeae* of SEQ ID NO: 2 as being structurally similar and having amino acid sequences that are 95 % identical. Within the first 178 amino acids of SEQ ID NO: 2 and SEQ ID NO: 4, there are only 3 amino acid differences, i.e., at amino acid positions 82, 89 and 90. Thus a reference to an amino acid fragment of aa1-178 of SEQ ID NO: 2 is submitted to clearly teach one of skill in the art an amino acid sequence of 1-178 of the specifically identified 95% identical homolog of SEQ ID NO: 4. However, the amended and new claims do not use the rejected language.

Double Patenting

Claims 3, 6 and 21 are rejected under the judicially created doctrine of obviousness-type double patenting over claim 1 of US Patent No. 6,610,306. Claims 4 and 5 are rejected for the same basis over claim 2 of said patent.

Cancellation of claims 3-6 renders application of this rejection moot as to them. Applicants respectfully request that the examiner allow Applicants to defer submission of

a terminal disclaimer in compliance with this ground for rejection for Claim 21 until allowable claim language has been determined.

35 USC §112, First Paragraph Rejection – New Matter

Claims 21-23 and 25 and the claims dependent thereon are rejected for allegedly containing subject matter not described in the specification, i.e., new matter. Specifically, the examiner rejects the language as being unsupported: antibodies to Neisseriae strains; suitable detectable label or detection system, antibodies that interfere with the binding of said Neisseriae strains to their cellular target, antibodies cross-reactive with multiple Neisseriae strains.

Applicants respectfully request reconsideration and withdrawal of these grounds for rejection in view of the extensive list of support in the specification provided with reference to the newly numbered claims on the preceding pages 7 and 8. All claim language used in the amended claims is supported in the original specification, including the figures. The support has been identified above by page, line number, figure reference, example number, *etc.*

The specification clearly teaches that antibodies induced by an OMP85 antigen of this invention recognized the OMP85 protein in multiple Neisseriae strains, i.e., from six representative strains of *N. gonorrhoeae* and four strains of *N. meningitidis*. See, page 48, lines 1-8 and FIG. 3. See, also, Example 7, at pages 50-52 and accompanying FIGs. 6, 7A and 7B. These examples clearly demonstrate that the OMP85 antigen can induce antibodies capable of binding the OMP85 proteins of multiple Neisseria strains, but not in the tested strains of Klebsiella, Pseudomonas, Salmonella, Shigella and E. coli. See page 52, last line through pg. 53, line 2.

Example 8 at page 53 also teaches that the antibodies induced by the OMP85 polypeptides of the invention binds to the surface of bacteria and interferes with the ability of the bacteria to adhere to the epithelial cells.

In view of the amended language of the claims, and the clear support of the application for language currently employed in the claims, Applicants respectfully

request that the examiner reconsider and withdraw this rejection as against any of the claims now pending.

35 USC §112, First Paragraph Rejection– Written Description/Enablement

Claims 21, 25-27, 2, 3 and claims dependent thereon are rejected for allegedly containing subject matter not described in the specification, i.e., lack of written description. The examiner states that the specification fails to teach a single polypeptide homolog that has the biological activity identified, such that the homolog composition when administered shows immunogenic activities or functions or diagnostic activity in vitro.

Claims 21-29, 2-7, 17 and 18 are rejected for allegedly failing to provide enablement for an immunogenic or diagnostic composition comprising a polypeptide from a homolog of SEQ ID NO: 4

Applicants respectfully request reconsideration and withdrawal of these grounds for rejection as against any of the currently pending claims in view of the amendments to the claims and the clear teachings of the specification, as discussed herein. Applicants submit that the specification both provides a clear written description and enablement for the compositions covered by independent claims 21, 25 and 50 and all claims dependent thereon.

Independent Claims 21 and 25 now require that their respective immunogenic or diagnostic compositions comprise an amino acid sequence of at least eight amino acids from within the *N. meningitidis* OMP85 amino acid sequence (SEQ ID NO: 4) in an amount sufficient to induce antibodies that recognize SEQ ID NO: 4 itself, as well as OMP85 proteins from multiple Neisserial species, as demonstrated by the specification. Thus, these claims no longer embrace "homologs".

New independent claim 50 provides for an immunogenic composition comprising a polypeptide having 95 % or greater sequence identity with the entire sequence of SEQ ID NO: 4, in an amount effective to induced antibodies to SEQ ID NO: 4. The remaining claims are dependent thereon and supported in the specification as indicated above. The specification provides sufficient written description of these embodiments as well as sufficient teaching to enable one of skill in the art to practice these inventions.

The specification clearly identifies two OMP85 polypeptides having 95% identity and 98% similarity in the specification, i.e., SEQ ID NO: 2 and SEQ ID NO: 4. The specification demonstrates in Fig. 5 exactly where the amino acid sequences for the two sequences differ. The specification further demonstrates that in addition to having substantially identical amino acid sequences, these two polypeptides have similar structures. Both sequences have identical signal sequences, as shown in Figs 2 and 5. and, as indicated in Example 6, both of the genes encoding these proteins have similarity in open reading frame flanking sequences, indicating conserved gene arrangements.

The specification thus shows that antibodies to SEQ ID NO: 2, which is a sequence having 95% identity to that of SEQ ID NO: 4, bind to the OMP85 of SEQ ID NO: 4. The examples of the specification demonstrate that antibodies induced by the OMP85 of *N. gonorrhoeae* SEQ ID NO: 2 were able to identify OMP85 sequences (for which the proteins had not yet been sequenced) from other *N. meningitidis* and *N. gonorrhoeae* strains. Antibodies generated to SEQ ID NO: 2 clearly recognize common conserved epitopes in six other *N. gonorrhoeae* and four other *N. meningitidis* strains tested, including the OMP85 sequence of SEQ ID NO: 4, which is the OMP85 protein obtained from *N. meningitidis* strain HH. See, page 47, line 3 and the OMP85 Western blot of "N. men. HH" in Fig. 6 and Figs. 7A and 7B. This evidence supports Applicants' claims to polypeptides having the biological activity of inducing antibodies that recognize OMP85 of SEQ ID NO: 4, as well as the OMP85 sequences of other *Neisseriae gonorrhoeae* and *meningitidis* strains. Example 8 of the specification further demonstrates that antibodies to the OMP of SEQ ID NO: 2 block binding of the bacteria to epithelial cells.

It is clear to the person of skill in the art that if a sequence sharing 95% sequence identity to a reference sequence can induce antibodies that bind the reference sequence, the reference sequence itself can be used to induce antibodies that bind to itself. Thus, the data in the specification clearly supports the specification's treatment of these two sequences as homologs having the same biological activity as taught by the specification,

i.e., to induce antibodies to bind the OMP85 sequence SEQ ID NO: 4 of *Neisseriae meningitidis* as well as other the other Neisseriae strains.

Further, the specification clearly teaches the use of fragments of from at least eight amino acids up to fragments just short of the 797 amino acid sequence of SEQ ID NO: 4 to accomplish the same biological activity as stated on pages 21-22. It is known to the art that sequences as short as those explicitly stated in the specification and even larger sequences can generate antibodies to the larger protein. For example, generation of antisera to variously sized protein fragments is clearly taught in publications such as Geysen *et al*, **1985** Proc. Natl. Acad. Sci., USA, 82:178-182; Shinnick *et al*, **1983** Ann. Rev. Microbiol, 37:426-446, at page 432; and Niman *et al*, **1963** Proc. Natl. Acad.Sci., USA, 80:4949-4953 among many others. Therefore as of the date of the present invention, it was known that small fragments could generate antibodies to the larger protein.

Given the explicit disclosure of the amino acid sequence of SEQ ID NO: 4, it is within the skill of the art to multiple generate fragments comprising at least 8 consecutive amino acids of SEQ ID NO: 4. Given the state of the art, and the examples of the specification, it is within the ability of one of skill in the art to generate antibodies to OMP85 fragments (see the N-terminal fragments used in Example 7) without undue experimentation. Finally, the ability of the generated antibodies to bind the OMP85 sequences can be readily tested by the means disclosed in the specification, e.g., as demonstrated both in Western assays of Examples 4 and 7, as well as in the cell adherence assay of Example 8.

Finally, a polypeptide that is 95% identical to the *entire* SEQ ID NO:4 is also capable of clear definition and enablement based on the disclosure of the specification. Not only is SEQ ID NO: 2 an example of such a polypeptide defined therein, but the specification identifies on pages 12, lines 12-22, algorithms that may be employed in determining sequence identity. Subsequent sequencing of OMP85 sequence in other *Neisseriae meningitidis* and *N. gonorrhoeae* strains has demonstrated that degree of

similarity predicted by the Western blot experiments of this specification. See the sequence comparison of now publicly accessible sequences attached hereto as Exhibit C.

It is not necessary for compliance with the enablement or written description requirements that every possible embodiment falling within the purview of the claims be exemplified within the specification. The task of the patent applicant is to ensure that the application teaches one of skill in the art how to make and use the claimed invention. Applicants respectfully submit that the detailed description and examples of this specification do accomplish exactly that function.

In fact, subsequent work by the inventor supports the data in the specification. For example, the inventor in a publication occurring after filing showed that antisera generated to variously sized fragments of SEQ ID NO: 4 was capable of binding to intact cells bearing the *N. gonorrhoeae* OMP85. See the powerpoint presentation of Judd (Document CJ) provided in the attached supplemental Information Disclosure Statement, particularly the slide labeled "Overlapping Subfragments of Neisserial OMP85 to be used to locate surface exposed regions able to react with anti-Omp85 sera".

In further support, Applicants also provide herewith as Exhibit A, a copy of a Declaration under Rule 132 by inventor Ralph C. Judd, executed October 16, 2002, and previously submitted in the prosecution of US Patent No. 6,610,306, which provided evidence that a peptide fragment of *N. meningitidis* OMP85, SEQ ID NO: 4, i.e., the first 178 amino acids thereof, was capable of generating antibodies that blocked the infection-initiating step in a gonnococcal cell adherence assay in the same manner that the *N. gonorrhoeae* OMP85 SEQ ID NO: 2 did in Example 8 of the present invention.

Thus, the two sequences that are 95% identical do share the ability to induce antibodies that bind Neisseriae OMP85 proteins.

In view of the amendments and indicated support for the original disclosure in this specification, Applicants request that these rejections based on lack of written description and lack of enablement be withdrawn and not maintained against the amended claims.

35 USC §112, Second Paragraph - Indefiniteness

Claims 21-29, 2-7, 17 and 18 are rejected as allegedly being indefinite for use of the terms "homolog", "effective amount", for reciting SEQ ID NO: 4 without the words "the amino acid sequence of", for use of the term "85% identity", for use of the term "fragment" in claim 5.

Applicants respectfully request reconsideration and withdrawal of this rejection in view of the amendment of the claims. Claims 21 and 25 and their dependent claims no longer uses the term "homolog". Claims using the indicator "SEQ ID NO:" now contain the preceding phrase "the amino acid sequence of" as required by the examiner. The term "fragment" is no longer used in favor of a polypeptide comprising at least 8 consecutive amino acids of SEQ ID NO: 4, which is submitted to be definite. The term "95% sequence identity" as used in claim 50 is clearly defined both by the Fig. 5 and in the specification at page 16, lines 18-21. The phrase "in an amount effective to induce antibodies that recognize SEQ ID NO: 4", while a functional definition, is readily determinable to one of skill in the art. Clearly compositions so characterized must contain polypeptides which are capable of inducing antibodies that bind SEQ ID NO: 4 and must contain sufficient of such polypeptide to actually induce such antibodies in the desired mammal. Clearly the determination of an effective amount requires an amount sufficient in a composition to induce detectable antibody response.. One cannot provide so small an amount to the proposed mammal's immune system that no response is detectable. A clinician should readily be able to determine a suitable amount based upon the nature of the mammal to be immunized, i.e., height, weight, body mass, general health, etc. Applicants respectfully submit that the amended claim language is indeed definite.

35 USC §102(a) Rejection

Claims 21-24 and 2-7are rejected as anticipated by Manning et al, Microb. Pathogen., 25:11-22 (1998), using Richarme et al, Ann. Microbiol. 133A:199204 (1982) to show that every element of the claimed subject matter is disclosed by Manning.

Applicants respectfully submit that this rejection may be removed on the basis of the attached Exhibit B, a copy of the *In re Katz* declaration previously submitted in the parent application. This declaration establishes that coauthors of Manning other than Drs. Judd and Manning, were not inventors of the present claims. This rejection may be withdrawn.

35 USC §102(b) Rejection

Claims 21-26, 2, 4, 5, 17 and 18 are rejected as anticipated by International Patent Publication No. WO 94/12641 (Chong et al) as evidenced by Harlow et al, in Antibodies: A Laboratory Manual, Cold Spring Harbor Laboratory, Ch 5, p 76 1988, US Patent No. 6,348,185 (Picwnica-Worms) or Protein Sequences on STN, pg. 12, because "homolog" has no structure or size limitation.

Chong discloses an isolated and purified 27 AA fragment of the D-15 polypeptide fused to a heterologous protein comprising the sequence DGVSLGGN of which DGVSLG is 100% identical to AA480-488 of SEQ ID NO: 4 and is therefore a "homolog" of SEQ ID NO: 4. The examiner states that the antibodies induced by Chong's fragment are expected to have the properties recited in the claims.

In view of the amendments and indicated support for the original disclosure in this specification, and particularly the removal of generic "homolog" language from Claims 21 and 25, neither Claim 21 nor 25, nor the pending claims dependent thereon encompass the fragments of Chong. Further, as Claim 50 requires that its polypeptides be 95% identical in sequence to the *entire* SEQ ID NO: 4, Claim 50 does not read on such small fragments as that of Chong. Applicants request that these rejections be withdrawn and not maintained against the amended claims.

35 USC §103 Rejection

Claims 25-29, 17 and 18 are rejected as allegedly obvious in view of Manning et al, cited above.

In view of the above-identified *In re Katz* declaration that removes Manning as an effective reference under 35 USC §102, Manning cannot be applied to make the present invention obvious. This rejection may now be withdrawn.

Documents cited by Examiner, not relied upon

Kawarabayasi *et al*, **1998** DNA Res, 5:55-76 refers to the sequence and gene organization of a hyper-thermophilic archaebacterium. Kawarabayasi teaches an eight AA sequence LGYDVYGK which matches AA485-492 of SEQ ID NO: 4. This fragment was found among the 2061 ORFs that were assigned to the entire genomic sequence. There is no suggestion at all of using any part of these newly sequenced genes or proteins or fragments thereof in an *immunogenic composition* for any reason.

Albertini *et al*, **1991** J. Bacteriol, 173:3373-3579 refers to the organization of a flagellar structure and ATPase-like polypeptide on *B. subtilis*. Albertini teaches the presence of an 8 AA sequence PNAETKTV which matches AA 328-335 of SEQ ID NO: 4 in the gene products. The only suggestion for use of such proteins is that the cloning and sequence will enhance *study* thereof (pg. 3578, col. 1). There is no suggestion at all of using any part of these newly sequenced genes or proteins in *an immunogenic composition* for induction of antibodies to any protein for any reason.

Supplemental Information Disclosure Statement

Applicants also provide herewith additional documents cited in a supplemental information disclosure statement for consideration by the examiner.

In view of the above amendments and remarks, Applicants respectfully request that the amended claims be permitted to issue in due course.

The Director is hereby authorized to charge any deficiency in any fees due with the filing of this paper or during the pendency of this application, or credit any

overpayment in any fees to our Deposit Account Number 08-3040.

Respectfully submitted,

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Attachments:

Exhibit A:	Declaration under 37 CFR §1.132 by R. Judd (prior patent)
Exhibit B:	In re Katz Declaration
Exhibit C:	OMP85 sequence comparison